

EXHIBIT 40

Brief Original Contributions

A CASE-CONTROL STUDY OF BORDERLINE OVARIAN TUMORS: THE INFLUENCE OF PERINEAL EXPOSURE TO TALC

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Harlow, B. L. (Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115), and N. S. Weiss. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol* 1989;130:390-4.

The authors interviewed 116 female residents of western Washington State with serous and mucinous borderline ovarian tumors diagnosed between 1980 and 1985 and questioned them on their use of hygienic powders. A sample of 158 control women from the same counties were identified through random digit dialing and were interviewed as well. Neither the perineal application of baby powder nor the perineal application of cornstarch was associated with an appreciably altered risk of borderline ovarian tumors. However, women who used deodorizing powders alone or in combination with other talc-containing powders had 2.8 times the risk (95% confidence interval 1.1-11.7) of women who had not had perineal exposure to powder. These results suggest that future studies of ovarian tumors in relation to the application of talc-containing powders should consider ascertaining the specific type(s) of powder used.

ovarian neoplasms; talc

In light of the marked differences in age-specific incidence and patient survival between borderline and malignant epithelial ovarian tumors (1), we conducted a case-control study of borderline ovarian tumors to determine whether etiologic differences between these low-grade tumors and their malignant counterparts exist as well. As part of this study, we sought to investigate the possible etiologic role of perineal exposure to talc.

Interest in talc as a potential ovarian carcinogen has grown from reports of oc-

cupational asbestos exposure and ovarian cancer (2-4). Mineral talc, similar in chemical composition to various asbestos minerals, is the common base for most dusting powders that women may apply to the perineum, sanitary napkins, or diaphragms prior to storage (5). Presently, three epidemiologic studies have examined the association between talc exposure and ovarian cancer (6-8).

MATERIALS AND METHODS

The Seattle-Puget Sound Cancer Surveillance System classifies borderline ovarian tumors according to the World Health Organization *International Classification of Diseases for Oncology* (ICD-O) (9). Female residents of three urban counties of western Washington State diagnosed as having a serous or mucinous borderline ovarian tumor (ICD-O codes 8,440-8,481) were identified from the files of this population-based cancer reporting system. Included were white women aged 20-79 years whose tumors were diagnosed during the years

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1980-1985. Among those tumors subject to an independent pathology review (73 per cent), 83 of 88 (94 per cent) were confirmed as borderline ovarian tumors. Given the high degree of histologic agreement, we chose to include the additional 33 cases whose tumors had not been reviewed. Through random digit dialing, we identified a control group of white women who were similar to the cases with respect to age and county of residence. Controls who had undergone bilateral oophorectomy were excluded from the analysis. Further details of the study methods are described elsewhere (10).

Reproductive, sexual, and medical histories and information on perineal exposure to talc were obtained during an in-person interview. An open-ended question asked women to specify the type(s), but not the brand name(s), of powder they had used for perineal application after bathing, on sanitary napkins, and for diaphragm storage prior to diagnosis (or a similar date for controls). Affirmative responses were categorized either as one or more of three talc-containing powders (baby powder, deodorizing powder, and other or unspecified talcum or "dusting" powders) or as cornstarch.

We were successful in obtaining interviews from 116 cases (68 per cent of those eligible) and 158 controls (74 per cent of those eligible). A detailed discussion of response rates can be found elsewhere (10). Since previous studies (including ours) have reported an association of ovarian cancer risk in relation to reproductive history and exogenous female hormones, we controlled for age, parity, and the use of oral contraceptives during the analysis, by means of stratification (11).

RESULTS

Women who reported any perineal use of dusting powders—either after bathing, on sanitary napkins, or for diaphragm storage—had an adjusted relative risk of 1.1 for developing a borderline ovarian tumor (95 per cent confidence interval (CI) 0.7-2.1) (table 1). We further examined this association according to both the specific

method of exposure to dusting powders and the type of powder used. The analysis by method of use indicates that a smaller proportion of cases than controls used talc-containing powder or cornstarch for diaphragm storage. The risk associated with the use of talc-containing powders or cornstarch after bathing was 1.2 (95 per cent CI 0.6-2.6). Women who reported any use of talc-containing powder or cornstarch on sanitary napkins had a risk about double (relative risk (RR) = 2.2, 95 per cent CI 0.8-19.8) that of women who reported no talc use. This risk was the same for women who reported applying powder both after bathing and to sanitary napkins. No increase in risk was present among short- and long-term diaphragm users, the risk was not modified by the use of cornstarch versus other talc-containing powders, and there was no variation in risk with increasing number of days of use (not shown).

When we compared cases and controls by the type of powder used, there was no excess risk of borderline tumors among women who applied cornstarch, baby powder, or unspecified talcum powder alone or in combination to the perineum. However, women who applied deodorizing powders with or without baby powder (only baby powder was reported as a second powder in women who used deodorizing powders) had nearly three times the risk of developing a borderline ovarian tumor compared with women who reported no perineal use of powder (RR = 2.8, 95 per cent CI 1.1-11.7).

When we examined the type of powder used according to the method of application, the excess risk due to the use of deodorizing powders was present regardless of whether it was applied after bathing or to sanitary napkins. No subjects reported any use of deodorizing powders for diaphragm storage.

DISCUSSION

Our results of perineal exposure to talc—no association among women who applied talcum powder to diaphragms, but a modest increase in risk among women who applied

TABLE 1

Perineal use of talc-containing powder and cornstarch among women with borderline ovarian tumors and their matched controls, by method of use and by type of powder used, western Washington State, 1980-1985

	Cases (n = 116)	Controls (n = 158)	Crude RR*	Adjusted RR†	95% CI*
No perineal exposure to powder	67	94	1.0‡		
Any perineal exposure to powder	49	64	1.1	1.1	0.7-2.1
Method of use					
Diaphragm storage only	8	21	0.5	0.5	0.2-1.4
Diaphragm storage only or with other methods	11	27	0.6	0.5	0.2-1.3
After bathing only	24	30	1.1	1.2	0.6-2.6
After bathing only or with other methods	34	37	1.3	1.3	0.8-2.7
Sanitary napkins only	7	4	2.5	2.2	0.8-19.8
Sanitary napkins only or with other methods	14	10	2.0	1.9	0.9-6.9
After bathing and on sanitary napkins	7	4	2.5	2.2	0.9-19.8
Type of powder used					
Cornstarch only (no combined use)	4	7	0.8	0.8	0.2-3.8
Baby powder only	18	31	0.8	0.8	0.4-1.9
Baby powder only or combined use	22	34	0.9	0.9	0.5-2.0
Talc, unspecified (no combined use)	13	19	1.0	1.0	0.4-2.4
Deodorizing powder only	10	4	3.5	3.5	1.2-28.7
Deodorizing powder only or combined use	14	7	2.8	2.8	1.1-11.7
Method and type of powder used					
Any powder use after bathing					
Any use of deodorizing powder	10	5	2.8	3.1	0.8-10.9
No use of deodorizing powder	24	32	1.1	1.1	0.5-2.4
Any powder use on sanitary napkins					
Any use of deodorizing powder	8	4	2.8	2.6	0.9-22.4
No use of deodorizing powder	6	6	1.4	1.5	0.4-6.5

* RR, relative risk; CI, confidence interval.

† Adjusted for age (20-39, 40-59, or 60-79 years), parity (nulliparous or parous), and use of oral contraceptives (ever or never).

‡ Reference group.

talc-containing powders to the perineum or to sanitary napkins—are consistent with those previously reported in studies of malignant ovarian tumors. Cramer et al. (6) observed a 50 per cent excess risk among women who used dusting powders or who applied talc-containing powders to sanitary napkins, and a relative risk of 3.3 among women who applied both. No association was found with use of talcum powder for diaphragm storage. Hartge et al. (7) also found no excess risk among users of talc for diaphragm storage, but they did report an association with perineal application

(seven cases, three controls; RR = 2.5, 95 per cent CI 0.7-10.0). Whittemore et al. (8) reported a 40 per cent excess in risk of ovarian cancer associated with perineal exposure only and a modest increase in risk with increasing numbers of applications per month.

An association between talc use and ovarian neoplasms seems biologically plausible, since particulates contaminating the vaginal area may migrate into the pelvic cavity and since particles of talc have been observed within ovarian tissue (12-15). It is also conceivable that the excess risk as-

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1-1.3

1-2.6

1-2.7

1-19.8

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sociated with application of talc to the perineum and to sanitary napkins that was seen in the three prior studies, none of which inquired about the type of powder, could have been due to a strong association restricted to the use of deodorizing powders. The lack of an increased risk among women who used talc-containing powder on diaphragms (both in our study and in the previous studies) supports this hypothesis, since deodorizing powder was infrequently used for diaphragm storage. Furthermore, differential asbestos contamination among different types of cosmetic talcum powders cannot be ruled out. Until 1975, US-manufactured cosmetic talcum powders were required to contain at least 90 per cent mineral talc, but until 1968, some products marked as cosmetic talcum powders did not conform to these guidelines (16, 17). In 1976, a study of 21 consumer talcum powders labeled as baby powders, facial powders, or body powders obtained from retail stores in New York City between 1971 and 1975 reported that 10 contained concentrations of asbestiform tremolite and anthophyllite ranging from 0.2 per cent to 14 per cent (4).

Although it is difficult to explain the lack of association among women who used baby powder exclusively, according to the product labels baby powder is reported to contain only talc and no other minerals or deodorizing substances. The product labels from deodorizing powders, body powders, and perfumed dusting powders, on the other hand, indicate that they contain deodorizing substances and a variety of other free and bonded silicas (potentially high in asbestiform fibers (18)) in addition to talc.

We suggest caution when interpreting the results of this study. The elevated risk among women who specifically used deodorizing powders could have been due to chance or applicable only to borderline, not malignant, ovarian tumors. We believe the latter possibility to be unlikely, since the risk associated with the use of any talc-containing powder was similar to that re-

ported in previous studies of women with malignant ovarian tumors. In addition, because of refusals and other reasons for non-participation, we were unable to include approximately 30 per cent of potentially eligible cases and controls. Since non-participants were similar to participants with respect to certain characteristics such as age and county of residence, we have no reason to believe that there was any dissimilarity in their use of talc-containing powders.

Given the clues provided by this study regarding the possible importance of deodorizing powders, it would be advisable for future studies to elicit information on the brand names of talc-containing powders and the timing and duration of use of each type of talc-containing powder. Although these data need replication, they raise the possibility that the risk of ovarian tumors in women who apply deodorizing powder to the perineum may not relate to talc per se but rather to asbestos contamination and/or a substance or substances used specifically for deodorization.

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